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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,131	02/14/2007	Wayne B. Harris	050508-1410	4639

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EXAMINER	
BAEK, BONG-SOOK	

ART UNIT	PAPER NUMBER
4161	

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09/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,131	HARRIS ET AL.	
	Examiner	Art Unit	
	BONG-SOOK BAEK	4161	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *1-27 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28,29 and 31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

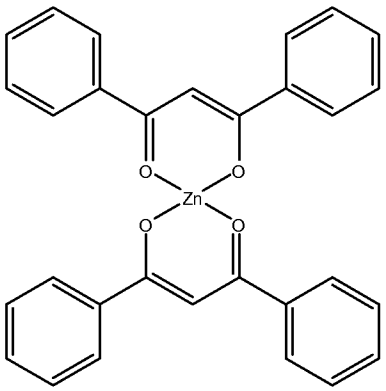
DETAILED ACTION

Status of Claims

Claims 1-33 are currently pending.

Election/Restrictions

Applicants' election of group III drawn to a method of modulating hypoxia inducible factor-1 (HIF-1) activity in a cell and election of species 1b, wherein the chemically defined HIF-1 inhibitor compound species have the following structure, in the reply filed on 6/16/2008 are acknowledged. The election was made without traverse:



Claims 1-27 and 30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group or species, there being no allowable generic or linking claim. Claims 28-29 and 31-33 are under examination in the instant office action.

Priority

The instant application is a 371 of PCT/US04/37090 filed on 11/8/2004, which claims priority from US provisional application 60/518146 filed on 11/07/2003. However, the provisional application does not provide support for all the compounds generically claimed in claims 3 and 6-14. Thus, the earliest effective U.S. filing date afforded the instantly claimed invention has been determined to be 11/8/2004.

Information Disclosure Statement

Information disclosure statement has not been filed yet.

Claim Objections

Claims 28-29 and 31-33 are objected because the claims are dependent from withdrawn claims. Applicant is required to cancel the claims, or amend the claims to place the claims in proper form, or rewrite the claims in independent form.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28, and 31-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. All dependent claims are included in this rejection.

Independent claims 28 and 31 recite "modulating". However, it cannot be determined what Applicants means by said "modulating" since there is no definition of "modulating" in the

specification or the claim and the word, "modulating" encompasses both upregulaitng and downregulating." It is unclear to the Examiner the metes and bounds of "modulating" as claimed in instant claims 28 and 31 and thus it renders the claim indefinite.

Claims 32-33 are rejected because they depend from claim 31; thus incorporate their limitation.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1) Claims 31-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing HIF-1 activity in protein level, does not reasonably provide enablement for modulating transcription of all genes with the claimed compounds. The claims contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. All factors have been considered together and specifically relevant factors are addressed below:

The nature of the invention. The instant invention is drawn to a method of modulating gene transcription with at least one bidentate zinc chelate compound.

The breadth of the claims: Claims 31-33 embrace modulating transcription of all genes, which may not be regulated through the HIF-1 with an HIF-1 inhibiting amount of at least one bidentate zinc chelate compound.

The state of the prior art: The level of skill in molecular biology is high. Gene transcription is a complicate process of transcribing DNA nucleotide sequence information into RNA sequence information, which involves multiple steps and is regulated by many different transcription factors. However, there is no record of modulating transcription of all genes through one transcription factor. In addition, there are conflicting results about the effect of zinc ion and dibenzoylmethane (DBM), which are reactants to form the above elected species ($Zn(DBM)_2$), on HIF-1. Mabjeesh *et al.* teaches DBM induces HIF-1α in protein level and increases expression of vascular endothelial growth factor (VEGF), which is one of genes associated HIF-1 (abstract, Biochem. Biophys Res Comm, 303:279-286, 2003). However, Chun *et al.* teaches HIF-1α mRNA isoform induced by zinc ion inhibits HIF-1 activity and reduce mRNA expressions of hypoxia-inducible genes (abstract and figure 1, J cell Sci, 114:4051-4061, 2001). Furthermore, Umbreit *et al.* teaches that the stable complex of DBM and Zn is an effective inhibitor of the hypoxic response by causing the rapid degradation of HIF-1α protein (abstract only, Proc Amer Assoc Cancer Res, 46, 2005).

The predictability or unpredictability of the art: The results of experiments in genetic engineering are unpredictable. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity

is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The Presence or Absence of Working Examples. Applicant does not provide any working examples and disclosure about modulating gene transcription with an HIF-1 inhibiting amount of at least one bidentate zinc chelate compound. The disclosure is limited to results about reducing HIF-1 protein level by co-administration of zinc ion and dibenzoylmethanate (Figures 15-16 and 18-19), not the exact compound claimed in the instant invention and does not provide any evidence correlating the downregulated HIF-1 activity with modulation of transcription of any gene. In addition, Applicants admitted that there was no effect on mRNA level (transcription) of HIF-1α by the co-administration of zinc ion and dibenzoylmethanate in the instant specification (p40, lines 20-28 and figure 17).

The Quantity of Experimentation Needed. In light of the discussion above, one of ordinary skill in the art would be required to conduct an undue amount of experimentation in order to reasonably and accurately determine whether all the claimed bidentate zinc chelate compounds would in fact effectively modulate gene transcription as claimed in the instant application without any guidance and working examples. Therefore, the enablement requirement is not satisfied.

2) Claims 28-29 and 31-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing HIF-1 activity in protein level with the elected compound, does not reasonably provide enablement for modulating gene transcription or downregulating HIF-1 in mRNA level with plethora of possibilities encompassed by the multiple formulae recited in claims 3 and 6-14. The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the relevant factual considerations.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). While all the above factors were considered, some of the specific considerations are described below:

The breadth of the claims: The claim is drawn to a method of using compounds defined by various formulae, which are allegedly useful in the modulation of gene transcription through HIF-1 and possibly for treatment of cancer. The multiple formulae in the claims are directed to substituents layered on top of substituents that vary independently and lead to compounds of a wide variety of structures. These compounds encompass molecules that widely vary in the physical and chemical properties such as size, molecular weight, acidity, basicity, and properties that are known in the art to greatly influence pharmacokinetic and pharmacodynamic parameters, not to mention the ability to productively bind to claimed biological target molecules. The number of theoretically conceivable compounds for the formula is in billions rendering the scope of the claims large.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for viability.

The amount of direction or guidance present: The guidance and direction provided in the application for making the claimed compounds is limited. With respect to the making aspect of enablement requirement, the specification is enabling for making some compounds such as elected species. It is not seen where in the specification enablement is for compounds other than the elected species. With regards to use aspect of the specification, the disclosure is limited to the results regarding effects of cotreatment of zinc ion and dibenzoylmethanate on HIF-1 protein level in vitro assay system (Figures 15-16 and 18-19). There is no disclosure or working example for modulating gene transcription including down-regulating HIF-1 transcription with claimed compounds in the instant specification. In the absence of prior art teaching, absence of citations (commercial or literature) for the procuring needed starting materials for the preparation, one skilled in the art attempting to make or use compounds of the present inventions would be faced with undue research burden.

The state and the predictability of the art: The pharmaceutical art is unpredictable and target compounds need to be individually assessed for viability. Extremely broad generalizations as found in the instant claims are in contradiction with the basis of quantitative structure-activity-relationship (QSAR). In spite of the narrow structural characteristics (see above) of the disclosed compounds, the biological activity seems to vary widely. As stated above in the first 112 rejection, the conflicting results have been shown by prior art (Mabjeesh *et al.* and Chun *et al.*) when zinc ion and dibenzoylmethane (DBM) are given separately. Thus it is unpredictable what specific embodiment of the billion possibilities of the instant claims would have the desired biological properties.

The quantity of experimentation needed: Based on the foregoing evidence, one of ordinary skill in the art would be presented with an unpredictable amount of research effort to identify a compound out of the plethora of possibilities encompassed by the instant invention that would have useful biological properties.

Genentech Inc. v. Novo Nordisk A/S (CA FC)42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Provisional Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 28-29 and 31-33 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 72-77 and 83 of U.S. Patent Application No. 10/983430. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the copending application claims and the instant claims are drawn to a method of modulating HIF-1 activity with bidentate zinc chelate compounds and the copending application claims anticipate the instant claims.

This is a provisional obviousness-type double patenting rejection.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BONG-SOOK BAEK whose telephone number is 571-270-5863. The examiner can normally be reached 8:00-5:00 Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BONG-SOOK BAEK
Examiner, Art Unit 4161

Bbs

/Patrick J. Nolan/

Supervisory Patent Examiner, Art Unit 4161